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Paper No. 11

UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

MAILED

MAY 28 2002

**Ex parte BASHIR ZIKRIA and
JEMAL ZIKRIA**

**PAT. & T.M. OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES**

Appeal No. 2001-1146
Application No. 08/837,840

ON BRIEF

Before LORIN, ADAMS and MILLS, Administrative Patent Judges.

LORIN, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1-20, all the claims pending in the application.¹

¹ Pursuant to 35 U.S.C. § 6(b), we review the adverse decision of the examiner. In doing so, we have considered the record, including:

- Final Rejection (paper no. 6);
- Brief (paper no. 9); and,
- Examiner's Answer (paper no. 10).

Claims 1, 19 and 20 are illustrative of the claims on appeal and read as follows:

1. Method of treating a human subject to prevent leakage of serum proteins from capillary endothelial junctions while simultaneously preventing the harmful effect of free radicals on cellular membranes and other organelles during a period of increased capillary permeability which comprises administering to a subject in need of such treatment an effective amount of a composition comprising at least one polysaccharide selected from the group consisting of hydroxyethyl starch and dextran and at least one antioxidant selected from the group consisting of superoxide dismutase, glutathione peroxidase, catalase, hydroxyethyl rutoside, cyclic adenosine monophosphate and vitamin C, in admixture with a pharmaceutically acceptable liquid carrier.

19. Method of treating a human subject to prevent leakage of serum proteins from capillary endothelial junctions during a period of increased capillary permeability and simultaneously preventing the harmful effects of free radicals on cellular membranes and other organelles which comprises intravenously administering to a subject in need of such treatment an effective amount of a composition comprising:

a) at least one polysaccharide consisting of hydroxyethyl starch and dextran and
b) at least one antioxidant selected from the group consisting of superoxide dismutase, glutathione peroxidase, catalase, hydroxyethyl rutoside, cyclic adenosine monophosphate and vitamin C,
in admixture with a pharmaceutically acceptable liquid carrier selected from the group consisting of 0.9% saline, 5% dextrose and Ringer's lactate and wherein said polysaccharide is present in an amount of about 5 to 12%.

20. A composition for treating a human subject to prevent leakage of serum proteins from capillary endothelial junctions while simultaneously preventing the harmful effect of free radicals on cellular membranes and other organelles during a period of increased capillary permeability which comprises at least one polysaccharide selected from the group consisting of hydroxyethyl starch and dextran and at least one antioxidant selected from the group consisting of superoxide dismutase, glutathione, catalase, hydroxyethyl rutoside, cyclic adenosine monophosphate and vitamin C, in admixture with a pharmaceutically acceptable liquid carrier.

The references relied upon by the examiner are:

Zikria U.S. 4,994,444 February 19, 1991

Weiss, "The Role of Superoxide in the Destruction of Erythrocyte Targets by Human Neutrophils," The Journal of Biological Chemistry, Vol. 225, No. 20, Issue of October 25, pp. 9912-9917, 1980.

Gerdin et al. (Gerdin), "Inhibitory effect of the flavonoid O-(β -hydroxyethyl)rutoside on increased microvascular permeability induced by various agents in rat skin," Int. J. Microcirc.:Clin. Exp. 1983, 2(1), 39-46; Chemical Abstracts, No. 99:47701p, p. 34.

Munkres et al. (Munkres), "Genetic control of cellular longevity in *Neurospora crassa*: A relationship between cyclic nucleotides, antioxidants, and antioxygenic enzymes," Age, (1984), 7/2 (30-35), EMBase Abstract No. 8418469.

Claims 1-20 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Zikria in view of Weiss, Munkres and Gerdin.

DISCUSSION

The parties agree that the claims stand or fall together. Accordingly, we will focus our attention on claim 1. It is directed to a

method of treating a human subject to prevent leakage of serum proteins from capillary endothelial junctions while simultaneously preventing the harmful effect of free radicals on cellular membranes and other organelles during a period of increased capillary permeability which comprises

- administering to a subject in need of such treatment an effective amount of a composition comprising
 - at least one polysaccharide selected from the group consisting of hydroxyethyl starch and dextran and
 - at least one antioxidant selected from the group consisting of superoxide dismutase, glutathione peroxidase, catalase, hydroxyethyl rutoside, cyclic adenosine monophosphate and vitamin C,
 - in admixture with a pharmaceutically acceptable liquid carrier.

Examiner has rejected claim 1 under 35 U.S.C. § 103 over Zikria in view of Weiss, Munkres and Gerdin.

The initial burden rests with the examiner to establish a prima facie case of obviousness of the claimed invention over the prior art. See In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992).

Examiner states that "Zikria discloses the use of hydroxyethyl starch and hydroxyethyl dextran as a means for treating human subjects to prevent leakage of serum proteins from capillary endothelial junctions (See abstract, columns 1-2 and claims 1-2)." Examiner's Answer, p. 3. This is not in dispute.

Zikria does not teach the claimed antioxidants. In that regard, examiner cites Weiss (superoxide dismutase, glutathione peroxidase, catalase), Munkres (cyclic adenosine monophosphate [cAMP]), and Gerdin (hydroxyethyl rutoside). Examiner (examiner's answer, p. 4) also states that "[v]itamin C is the world [sic: world's] best known naturally occurring antioxidant which even the non-artisan would recognize immediately as an antioxidant." Accordingly, examiner makes the case that each and every claimed antioxidant is known in the art.

Based on the teachings described above, examiner (examiner's answer, pp. 4-5) concludes:

Therefore, it would have been obvious to the person of ordinary skill in the art at the time of the invention to have modified Zikria's method of preventing leakage of serum proteins from capillary endothelial junctions during increased capillary permeability and the compositions of hydroxyethyl starch used therein, by adding one or more of the art recognized, non-toxic antioxidants taught by Weiss, Munkres, or Gerdin or otherwise known by the public (i.e., vitamin C) for the expressed purpose of protecting all cells of the

body, including the cells that form the capillary endothelial junctions from oxidative and free radical damage that would increase membrane permeability, and thus lead to leakage of serum proteins.

The issue for our determination is whether one of ordinary skill in the art viewing the disclosures of the secondary references would be led to modify the process set forth in Zikria to include one of the antioxidants disclosed therein and thereby derive the claimed invention.

Appellants argue (brief, p. 7) that there is no suggestion in the prior art to combine the claimed materials.

In response to appellant's argument, examiner argues that - with regard to Weiss (superoxide dismutase, glutathione peroxidase, catalase), Munkres (cyclic adenosine monophosphate [cAMP]), and vitamin C - "[p]rotecting all body cells from further oxidative and free radical stress by giving non-toxic antioxidants known to protect cells from oxidative free radical damage, would certainly seem to be eminently reasonable and logical" (examiner's answer, p. 6). With regard to Gerdin (hydroxyethyl rutoside) which teaches the rutoside for inhibiting microvascular permeability, examiner argues that the "combination of hydroxyethyl starch with a second compound also known to reduce microvascular permeability would have been obvious to the artisan wanting to obtain the combined benefits of two compounds that reduce the leakage serum proteins at capillary endothelial junctions" (examiner's answer, p. 8).

The crux of examiner's argument is that the claimed antioxidants are known and have a known function to either protect cells from oxidative free radical damage or, in the case of hydroxyethyl rutoside, inhibit microvascular permeability. Therefore, according to examiner, absent unexpected results, it would have been obvious to include any of these substances with Zikria's hydroxyethyl starch/dextran to obtain a combination of known effects attributable to both the antioxidant and the hydroxyethyl starch/dextran.

There are a number of difficulties with examiner's reasoning. First, the claimed process of claim 1 requires treating a human subject "during a period of increased capillary permeability." Nowhere does examiner show that it is known to give a human subject an antioxidant during such a period. Second, examiner makes a number of generalized statements about the function of antioxidants that are not shown in the cited prior art². Third, examiner has not established that it is known to combine an antioxidant with another substance, let alone with a substance that would prevent leakage of serum proteins from capillary endothelial junctions. And, fourth, even if, assuming arguendo, the antioxidants that are claimed possess the generalized properties examiner suggests they

² For example, examiner (examiner's answer, p. 7) states that:

In this case the motivation to combine comes from the knowledge generally available to the artisan that it is prudent to protect the all the cells of a person from free radical damage by administering antioxidants, otherwise known as free radical scavengers. Even when there is no immediate emergency, millions of people take antioxidants like vitamin C and vitamin E in order to prevent oxidative damage and free radical damage to their cells, and thus, to maintain good general health. **However, for the person who has experienced trauma, when speed of treatment is critical, adding an antioxidant like vitamin C to the i.v. drip allows for more rapid distribution throughout the body for immediate benefit** [our emphasis].

have and that it is known to combine the claimed antioxidants with other pharmaceuticals, it is not entirely clear that the properties said to be associated with each substance would still be retained when combined with Zikria's hydroxyethyl starch/dextran. Because of these gaps in reasoning, examiner fails to adequately demonstrate how one of ordinary skill reading the references would be led to modify the Zikria method such that it would include any one of the substances disclosed in the secondary art and thereby derive the claimed invention.

The question is not whether it is known to use antioxidants to prevent cell damage, which, arguably, is known per se, or to use Gerdin's hydroxyethyl rutoside to inhibit microvascular permeability, but rather, what would lead one of ordinary skill to modify Zikria to include one of the substances of the secondary references? We fail to find any reason why one of ordinary skill reading these references would consider adding any of these substances as part of Zikria's method of preventing leakage of serum proteins from capillary endothelial junctions. Examiner has not shown, for example, that Zikria recognizes that there exists a problem of cell damage due to oxidative free radicals which might be overcome by using the substances of the secondary art. The mere fact that the prior art could be modified to obtain the claimed process does not make the modification obvious unless the prior art suggested the desirability of the modification. In re Gordon, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984). "To establish a prima facie case of obviousness based on a combination

of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant." In re Dance, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998). It does not suffice to say, for example, that "the motivation to combine comes from the knowledge generally available to the artisan that it is prudent to protect all the cells of a person from free radical damage by administering antioxidants, otherwise known as free radical scavengers" (examiner's answer, p. 7) as examiner has. Something in the prior art as a whole must suggest the desirability of combining hydroxyethyl starch/dextran with one of the prescribed antioxidants and thus the obviousness of making that combination. Lindemann Maschinenfabrik GmbH v. American Hoist and Derrick Co., 730 F.2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984).

The only reason we can find for modifying Zikria, by including one of the prescribed antioxidants, is in the specification. Therein (p. 1) it states that the invention is directed to

... preventing leakage of macromolecules from capillary endothelial junctions during a period of increased capillary permeability secondary to burn injury, cytotoxicity, trauma, septic and hemorrhagic shock, ischemia and other inflammatory processes and at the same time preventing pathology due to the activity of free radicals.

In using the dual-substance composition that is claimed, appellants are able to obtain a simultaneous preventative treatment. However, it is impermissible to use the disclosure from appellant's specification as a blueprint to reach the claimed invention from the prior art disclosure. "When prior art references require

selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself." Uniroyal Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044, 1051, 5 USPQ2d 1434, 1438 (Fed. Cir.), cert. denied, 118 S.Ct. 1548 (1988). Nevertheless, one cannot rely on appellant's disclosure to support a case of obviousness. "Obviousness can not be established by hindsight combination to produce the claimed invention," In re Dance, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998). Accordingly, we conclude that the examiner has not met the burden of establishing a prima facie case of obviousness of the claims over Zikria in view of Weiss, Munkres and Gerdin.

The rejection of claims 1-20 is reversed.

REVERSED


HUBERT C. LORIN)
Administrative Patent Judge)


DONALD E. ADAMS)
Administrative Patent Judge)


DEMETRA J. MILLS)
Administrative Patent Judge)

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